vided by instillation into the nares of 1% lidocaine and by administering 1% lidocaine onto the larynx and vocal cords, trachea, and lower airway through the bronchoscope channel. A narcotic such as meperidine or fentanyl and midazolam, provided in carefully titrated doses, may also be used. Skill in airway management and respiratory support is required, and monitoring and an environment conducive to ongoing assessment and intervention are essential.

In the outpatient setting, flexible bronchoscopy is commonly done to evaluate airway anatomy. Laryngomalacia, the most common finding in infants with stridor, is easily demonstrated by the dynamic view of the larynx provided by the fiberoptic endoscope. Unilateral or bilateral cord dysfunction, glottic hemangiomas, and laryngeal cysts are easily detected by fiberoptic studies. Tracheomalacia is often associated with laryngomalacia and is well visualized after the bronchoscope is passed into the trachea. Vascular compression of the trachea is also easily recognized, as are other malformations in lower airway anatomy. Persistent wheezing in an older child may be an indication for bronchoscopy, especially if there is evidence of localized disease or a low probability of a history of foreign body aspiration. Rigid bronchoscopy rather than flexible bronchoscopy is, however, indicated for foreign body removal in children. In addition, rigid bronchoscopy is required for the biopsy of endobronchial lesions and is preferred when difficulty in establishing or maintaining the airway is anticipated.

Laryngoscopy and bronchoscopy are equally useful procedures in children admitted to hospital. Infants with chronic lung disease are at risk for subglottic stenosis and lower airway lesions including endobronchial granulations, bronchial stenosis, tracheomalacia, and bronchomalacia. Optimal treatment can be provided when these conditions are diagnosed. Flexible laryngoscopy can be used in intensive care units to evaluate the upper airway before or during extubation. It is particularly useful in evaluating the resolution of epiglottitis and in evaluating laryngeal injury following prolonged intubation or inhalation injury.

Bronchoscopy and bronchoalveolar lavage have proved to be particularly useful in diagnosing *Pneumocystis carinii* pneumonia in children with human immunodeficiency viral infection. Bronchoalveolar lavage is also useful in the diagnosis of pneumonia in children whose immune system is compromised by chemotherapy or other causes and in the evaluation of chronic radiographic infiltrates in children with chronic lung disease of unknown cause.

Complications of flexible laryngoscopy and bronchoscopy are generally infrequent. Minor complications occur in 2% to 3% and include epistaxis, transient bradycardia, and adverse reactions to anesthetic agents. Major complications, which include infection, pneumothorax, and laryngospasm, occur in about 0.4% of lower airway examinations. Death has been reported but is such an infrequent occurrence that it is rare even in large series.

Further applications and improvements in technique and instrumentation can only be expected as pediatric flexible bronchoscopy enters its second decade.

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Bone Marrow Transplantation for the Treatment of Genetic Disease

BONE MARROW TRANSPLANTATION, the treatment of choice for various genetic diseases, may be efficacious for three categories of these diseases. The first is one in which the defect is expressed in the marrow stem cell, such as in patients with severe combined immunodeficiency disease. This disorder is the result of a congenital defect in lymphocytes in which the chances of surviving beyond 1 to 2 years of age without a bone marrow transplant are virtually zero, whereas 75% to 80% of children will be cured with its use. Until recently, only a relatively small number of these children could benefit from a bone marrow transplant because of the lack of histocompatible donors. With the development of techniques for depleting partially matched parental bone marrow of T cells, however, virtually every child with severe combined immunodeficiency now can be offered a curative bone marrow transplant. Other congenital marrow stem cell defects for which the procedure has been used include β-thalassemia major, Wiskott-Aldrich disease, chronic granulomatous disease, and osteopetrosis.

The second category of genetic disease is one in which the defect is expressed in all tissues but involves mostly the marrow stem cell population. For example, adenosine deaminase deficiency and nucleoside phosphorylase deficiency, both of which result in severe combined immunodeficiency, and glucocerebrosidase deficiency, which results in Gaucher's disease, are disorders that principally involve bone marrow-derived lymphocytes and mononuclear phagocytes, respectively. Bone marrow transplantation with the successful replacement of these hematopoietic cells can significantly ameliorate the manifestations of these disorders.

The third category of genetic diseases for which bone marrow transplantation may be indicated includes those in which the defect is expressed in all tissues and there is substantial systemic disease involving many organs. The rationale for a bone marrow transplant in these patients is dependent on marrow-derived tissue histiocytes including Kupffer and Ito cells in the liver; Langerhans cells in the skin; microglia cells in the central nervous system (CNS); osteoclasts in the bones; and macrophages in the lung, spleen, lymph nodes, tonsils, and peritoneum. These marrow-derived cells of donor origin can repopulate affected organs in the recipient and provide a new source of enzyme activity. The lysosomal storage diseases are in this third category of genetic disease. More than 100 children with various lysosomal storage diseases have received a bone marrow transplant. Nearly half were children with Hurler's mucopolysaccharidosis, an autosomal recessive disorder affecting the enzyme α-L-iduronidase. Clinical manifestations of Hurler's syndrome include CNS deterioration, growth failure, joint disability, organomegaly, myocardial or cardiac valvular disease, upper airway obstruction with sleep apnea, corneal clouding, and hearing loss. Patients usually die within the first decade of life with mental retardation and severe cardiopulmonary disease. Bone marrow transplantation has been successful in lessening many of the manifestations of this disease and substantially altering its natural history. The dysmorphologic facial and body features are ameliorated, joint function is improved, and the cardiopulmonary abnormalities and organomegaly abate. In terms of the CNS disease, hydrocephalus does not progress or, in some patients, does not develop, and in more than half of the patients there has been no further deterioration in mental state. Whether the successful results of

bone marrow transplantation in Hurler's syndrome will be repeated in other lysosomal storage disorders is unknown, and resolving this question will require carefully controlled clinical trials.

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Fetal Surgery

MOST PRENATALLY DIAGNOSED correctable malformations are best managed by appropriate medical and surgical therapy after maternal transport and planned delivery at term. A few simple anatomic abnormalities with predictable developmental consequences may be corrected before birth, however.

Fetal urethral obstruction interferes with the development of the fetal kidneys and lungs. Studies of animals have shown that obstruction produces renal dysplasia and pulmonary hypoplasia due to oligohydramnios, and these often fatal consequences can be ameliorated by decompression before birth. The natural history of fetal urinary tract obstruction has now been well documented by the sonographic follow-up of untreated cases, and selection criteria have been developed based on the ability to predict fetal renal function from fetal urine electrolyte levels and the sonographic appearance of the fetal kidneys. Although most fetuses do not require intervention, a fetus with bilateral hydronephrosis due to urethral obstruction in whom oligohydramnios develops may benefit from either early delivery and postnatal decompression if the lungs are mature or, if the lungs are immature, in utero decompression either by a catheter shunt placed percutaneously under sonographic guidance or by open fetal intervention to create a fetal vesicostomy. Several hundred fetuses have now been treated. It is clear that improvements in selection make it possible to avoid intervention in most cases and that decompression of an obstructed fetal urinary tract can prevent the development of fatal pulmonary hypoplasia.

Most babies born with congenital diaphragmatic hernia die of pulmonary insufficiency despite optimal postnatal care because their lungs are hypoplastic from intrauterine compression by herniated bowel. Despite more optimistic reports from children's referral centers, which see only the patients who survive transport, the mortality for diaphragmatic hernia diagnosed in utero is approximately 80% based on sonographic follow-up of more than 200 cases. There is a wide spectrum of severity, and some mildly affected children do well with conventional treatment. An algorithm for management has been presented that selects severely affected babies on the basis of a dilated stomach in the chest, mediastinal shift by a large volume of herniated viscera, and the development of polyhydramnios. For severe lesions detected before 24 weeks of gestation, repair before birth is possible. Extensive experimental work in fetal lambs and monkeys has shown that repair before birth is physiologically sound, technically feasible, and can be accomplished with safety for the mother and her reproductive capacity. The repair is technically difficult, and the first attempts in human fetuses failed because of an unanticipated problem with herniation of the fetal liver and kinking of the umbilical vein. The technical problems have proved surmountable, however, and several babies are now thriving after successful in utero repair.

Several other simple anatomic problems may be amenable to repair before birth. Although most cystic adenomatoid malformations of the lung can be corrected after birth, fetal hydrops can develop in fetuses, with large lesions causing significant compression of normal lungs and causing them to die in utero, a sequence that may be reversed by removing the abnormal pulmonary tissue. Some fetuses with large sacrococcygeal teratomas have high-output cardiac failure and hydrops and die in utero—again, a sequence that can be reversed only by interrupting the vascular steal either by occluding the vessels to the tumor or removing the tumor before birth. Simple obstructions to intracardiac blood flow may be amenable to fetal intervention, such as a recent attempt to dilate a stenotic aortic valve before birth. Some fetuses with heart block unrelated to anatomic abnormalities with ventricular rates slow enough (<45 beats per minute) to cause hydrops and fetal death may benefit from electrical pacing in utero. One of the most interesting observations to arise from experimental and now clinical fetal surgery is that the fetus heals without scarring or fibrosis. Unraveling the mechanisms of scarless healing in the fetus may allow therapies that improve healing after birth. Intervention for disfiguring but not life-threatening anomalies such as cleft lip and palate and craniofacial anomalies is not warranted at present, however. Fetal intervention is the logical culmination of advances in fetal diagnosis, and new applications are rapidly evolving.

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Predictors of and New Therapy for Jaundice

IN SICK, PREMATURE, or severely jaundiced infants, the evaluation of risk for brain injury caused by bilirubin should include the measurement of arterial blood gas pressures, albumin level, and total serum bilirubin level. In a term infant with normal arterial pH and without hemolytic disease, the total binding capacity (in milligrams per deciliter) should probably not exceed the albumin concentration (in grams per deciliter) more than seven times. For example, if an infant has an albumin level of 3.4 grams per dl, an exchange transfusion should be done if the bilirubin level reaches 23.8 mg per dl (3.4×7). Using Système International (SI) units, the multiple should be 12: 34 grams per liter (albumin) $\times$ 12 = 408 μmol per liter (bilirubin). In very sick infants, the quality of albumin binding may be impaired, and a multiple of 5 to 6 times the albumin concentration might yield a more appropriate estimate of risk (9 to 10 $\times$ using SI units). Because the tissue deposition increases linearly with the hydrogen ion concentration, aci-